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EDITORIAL

# Using toxidromes in the ICU

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Managing poisoned patients is challenging and requires the identification of clinical/paraclinical findings to initiate specific treatments while toxicological evidence is pending. The toxidrome-based approach is a heuristic method providing syndromic frameworks for identifying poisoning caused by substances with similar toxic effects, often sharing the same mechanisms of toxicity [1]. In this toolbox, we present the toxidrome-based approach, its strengths and limitations, and the most frequently encountered toxidromes in clinical practice.

## Usefulness of toxidromes

In the ICU, toxidromes help clinicians:

- to quickly identify the likely toxicant class, initiate immediate specific treatment when available, and guide clinical monitoring in *poisoned patients,*
- to monitor for early signs of poisoning in *exposed but asymptomatic patients.*

## How to use toxidrome: a stepwise approach (Fig. 1)

### Vital signs

Collect body temperature, respiratory and heart rate, and blood pressure. The interpretative value of vital sign abnormalities increases with the extent of deviation from normal values.

### Physical examination

Perform a complete clinical examination focusing on

- Neurologic: pupil size, abnormal movements, muscle tone, and reflexes. Changes in mental status are often prominent but nonspecific.
- Extra-neurologic: respiratory, gastrointestinal, urinary, and cutaneous systems.

### Bedside clinical tests

Always perform an electrocardiogram. Obtain bedside capillary glucose in case of impaired consciousness. Blood gas is commonly indicated to assess severity.

### Synthesize the findings to identify toxidrome considering limitations

Before interpreting your findings using Fig. 1 and the next two sections, you should consider that:

- Toxidromes are usually assessed dichotomously (present/absent), but poisoning is a dynamic *continuum of toxic effects* [2].
- Toxidrome sensitivity and specificity are imperfect [3]. Toxidromes may be incomplete, with key features missing, hindering accurate diagnosis. Many toxidromes share symptoms with other critical conditions.
- More than one toxidrome may be observed in the same patient [3]:
  - identifying a toxidrome is challenging in mixed ingestions; sometimes opposing effects can occur ("speedball", sympathomimetic and opioid).
  - many drugs overlap in classes: phencyclidine may cause initial sedation (NMDA receptor antagonism) and then sympathomimetic toxidrome; tricyclic antidepressants can trigger both anticholinergic and sodium channel blocker toxidromes [4]; some new psychoactive substances (synthetic cannabinoids, amphetamine analogues) also have unique effects.

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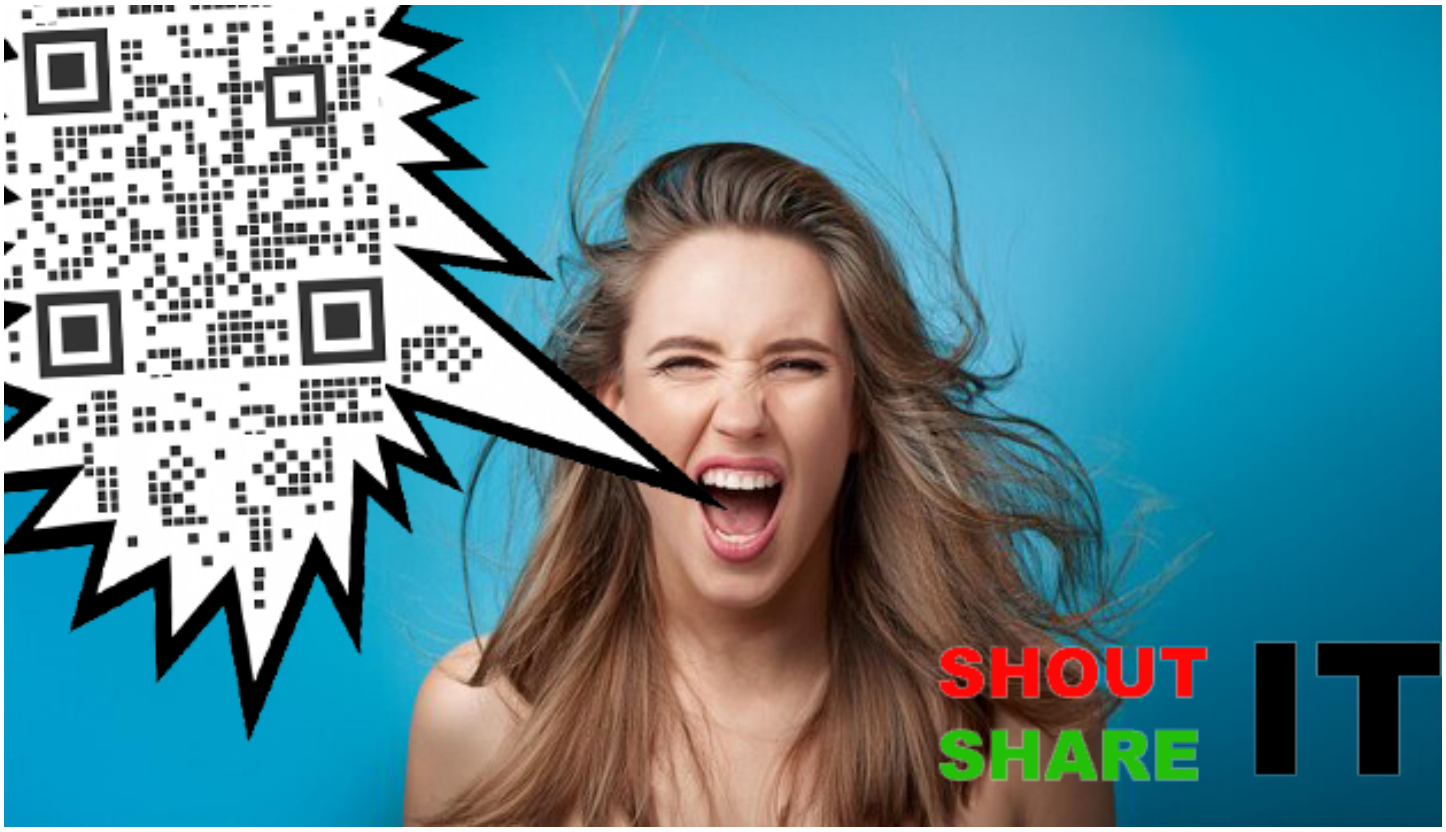
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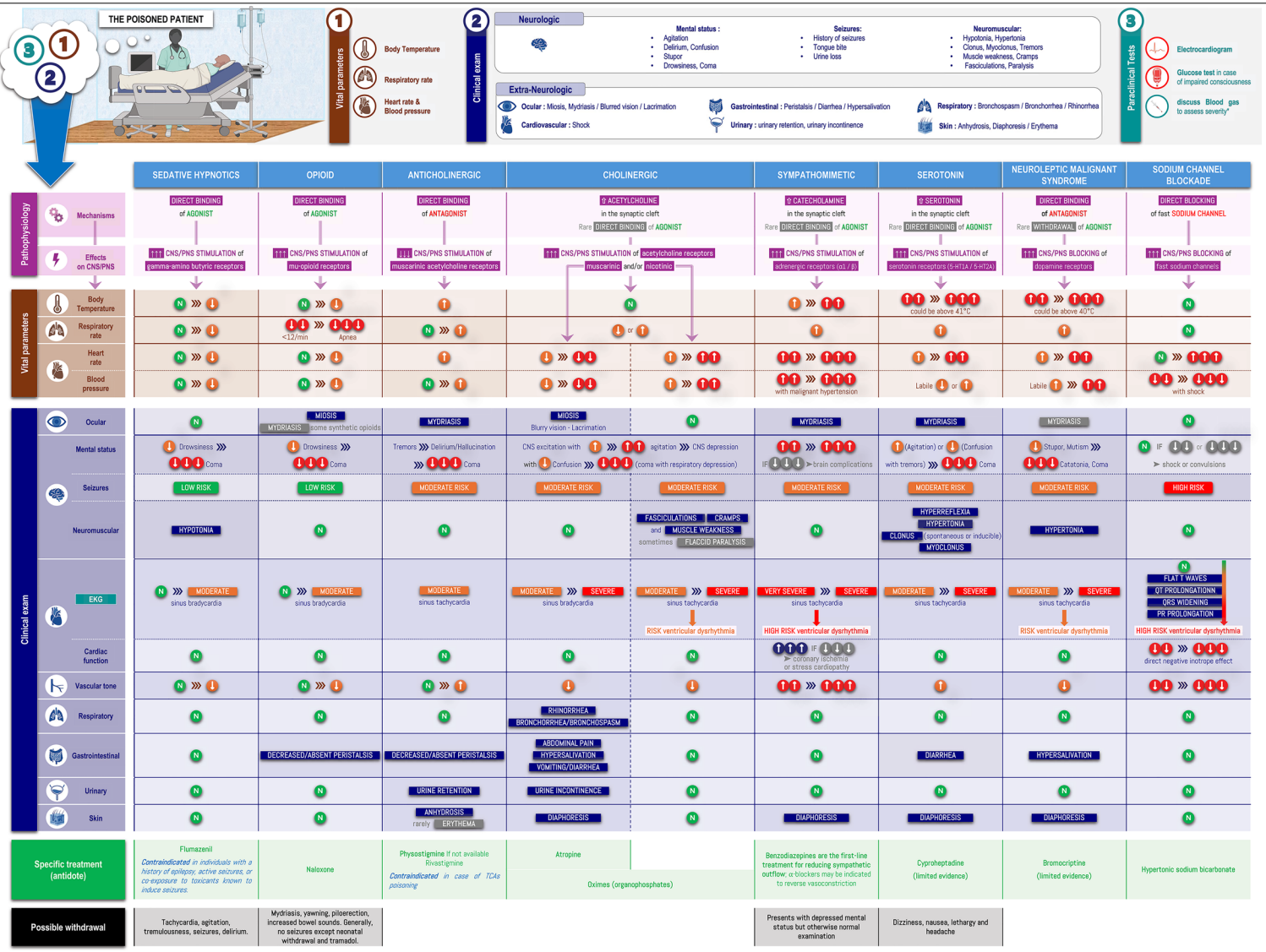


**Fig. 1** Description of the toxidromes most frequently encountered in clinical practice. The blue color represents common symptoms while gray shows an inconsistent effect. The green indicates no effect, orange represents a moderate effect, and red indicates a severe or very severe effect. *Blood gas is often indicated to assess severity. Certain blood gas abnormalities can guide the diagnosis of poisoning in the ICU. A high anion gap acidosis without hyperlactatemia may suggest toxic alcohol poisoning or early salicylate poisoning, severe hyperlactatemia may suggest metformin or cyanide poisoning, and respiratory depression may suggest opioid poisoning. However, blood gas abnormalities, particularly hyperlactatemia, are common in the ICU and are most often related to non-toxic causes in critically ill patients. *CNS* central nervous system, *PNS* peripheral nervous system, *STEMI* ST elevated myocardial infarction, *TCAs* tricyclic antidepressants. The figure was partially created with Biorender

- Sedative-hypnotic withdrawal can mimic sympathomimetic poisoning, and sympathomimetic withdrawal can mimic sedative-hypnotic poisoning, but treatment is similar (benzodiazepines and supportive care respectively). Other withdrawal syndromes (opioid, serotonin) may suggest poisoning but can be distinguished by context and clinical manifestations (Fig. 1).
- In the ICU, assessing neurological changes in sedated patients, especially under neuromuscular blockade, is challenging, and some treatments can cause toxidrome symptoms (opioids and miosis).

## Classic toxidromes (Fig. 1)

"*Classic toxidromes*" historically identified substances directly (agonist/antagonist) or indirectly (increased synaptic monoamines) interacting with the same receptor in the nervous system [1, 3, 5].

### Sedative/hypnotic and opioid

Both result in depressed mental status.

#### *Sedative/hypnotic [5]*

- **Toxicants**: often γ-aminobutyric acid type A receptor agonists (ethanol, benzodiazepines); other receptors may be involved.
- **Key features**: coma not associated with other clinical/vital signs abnormalities.
- **Severity**: complications from coma.

#### *Opioid [6]*

- **Toxicants**:
  - μ-opioid receptors agonists,
  - ketamine and γ-hydroxybutyrate can mimic opioid toxidrome [7, 8].
- **Key features**: coma, miosis and bradypnea (< 12/min), the most specific symptom.
- **Severity**: complications from coma, depth of hypoventilation.

### Anticholinergic and sympathomimetic

Both result in tachycardia, hyperthermia, mydriasis, agitation/delirium and an increased risk of seizures.

#### *Anticholinergic [5]*

- **Toxicants**: muscarinic acetylcholine receptors antagonists (nefopam, scopolamine, datura).
- **Key features**: mydriasis with non-reactive pupils, delirium, moderate hyperthermia, moderate tachycardia/hypertension, anhidrosis, frequent urine retention.
- **Severity**: depends on the patient's condition (often elderly) and the agent involved (tricyclic antidepressants (TCAs) can also cause a sodium channel blocker toxidrome).

#### *Sympathomimetic [5]*

- **Toxicants** elevating norepinephrine in the synaptic cleft (amphetamine, cocaine, monoamine oxidase type A inhibitors); rarely, α1 (methoxamine, ergot alkaloids) or β (salbutamol, terbutaline) adrenergic receptor agonists.
- **Key features**: mydriasis with reactive pupils, agitation, moderate to severe hyperthermia, prominent severe tachycardia and hypertension, diaphoresis.
- **Severity**: primarily cardiovascular complications (ischemia, dysrhythmia), severe hyperthermia.

### Serotonin and NMS

Both result in agitation/delirium, hyperthermia, hypertonia and an increased risk of seizures.

#### *Serotonin [9]*

- **Toxicants** elevating serotonin in the synaptic cleft (cocaine, MDMA, monoamine oxidase type A inhibitors, SRIs); rarely, serotonin receptor agonists (buspirone, triptans).
- **Key features**:
  - Hunter's criteria: in addition to agitation and hyperthermia > 38 °C, combination of various signs among clonus (spontaneous/inducible, ocular), diaphoresis, tremor, hyperreflexia, and hypertonia. Spontaneous clonus, particularly ocular clonus, is the most specific symptom.
  - Other: mydriasis, labile hypertension with tachycardia, hypersalivation.
  - Rapid onset (hours-days)
- **Severity**: severe hypertonia with rhabdomyolysis masking generalized seizures and clonus, hyperthermia over 42 °C responsible for fatal shock, multiorgan failure, and disseminated intravascular coagulation.

#### *Neuroleptic malignant syndrome [10]*

- **Toxicants** inducing excessive dopamine receptor antagonism (antipsychotics, withdrawal from antiparkinsonian agents) resulting in functional dopamine depletion.

- **Key features**: share most of the symptoms of the serotonin toxidrome, but
  - Infrequent mydriasis,
  - Delirium and stupor rather than agitation,
  - Specific "lead-pipe" hypertonia
  - No clonus, no hyperreflexia.
  - Gradual onset (days-weeks)
- **Severity**: severe hypertonia with rhabdomyolysis, severe hyperthermia.

### Cholinergic [11]

Rarely poses a diagnostic challenge.

- **Toxicants** reducing synaptic degradation of acetylcholine by cholinesterase inhibitors (organophosphates, anticholinesterase drugs); rarely, muscarinic (mushrooms, pilocarpine) or nicotinic (nicotine) receptor agonists.
- **Key features**: the clinical picture is rarely complete and results from the inhibition of
  - Peripheral muscarinic receptors: miosis, blurred vision, bronchospasm, abdominal pain, urine incontinence,
  - Peripheral nicotinic receptors: fasciculations, cramps, weakness, tachycardia, hypertension,
  - Central acetylcholine receptors: excitation followed by reduced consciousness, multifactorial seizures.
- **Severity**: central/peripheral respiratory impairment, multifactorial aspiration pneumonia.

### Extended toxidromes

*"Extended toxidromes"* emerged as important toxicity patterns to identify with accessible paraclinical tests, sometimes involving specific interactions with molecular structures beyond receptors.

#### *Sodium channel blockade [12]*

- **Toxicants** directly blocking fast sodium channels (TCAs, Vaughan–Williams Ia and Ic antiarrhythmics, diphenhydramine).
- **Key features**:
  - Cardiovascular: primarily altered heart action potential conduction with ultimately QRS widening (Fig. 1) often associated with multifactorial shock (negative inotropic effect, vasoplegia).
  - Other: seizures, acute respiratory distress syndrome.
- **Severity**: dysrhythmia, sudden cardiac arrest, multifactorial refractory shock.

## Conclusions

Although imperfect, the toxidrome-based approach remains a pragmatic diagnostic strategy in unknown poisonings, often permitting rapid treatment despite limited available information.

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**References**
1. Mofenson HC, Greensher J (1974) The unknown poison. Pediatrics 54:336–342. https://doi.org/10.1542/peds.54.3.336
2. Isbister GK, Buckley NA, Whyte IM (2007) Serotonin toxicity: a practical approach to diagnosis and treatment. Med J Aust 187:361–365. https://doi.org/10.5694/j.1326-5377.2007.tb01282.x
3. Nelson L (2019) Goldfrank's toxicologic emergencies, 11th edn. McGraw-Hill Medical, New York
4. Goldgran-Toledano D, Sideris G, Kevorkian J-P (2002) Overdose of cyclic antidepressants and the Brugada syndrome. N Engl J Med 346:1591–1592. https://doi.org/10.1056/NEJM200205163462020
5. Holstege CP, Borek HA (2012) Toxidromes. Crit Care Clin 28:479–498. https://doi.org/10.1016/j.ccc.2012.07.008
6. Boyer EW (2012) Management of opioid analgesic overdose. N Engl J Med 367:146–155. https://doi.org/10.1056/NEJMra1202561

7. Schep LJ, Slaughter RJ, Watts M et al (2023) The clinical toxicology of ketamine. Clin Toxicol (Phila) 61:415–428. https://doi.org/10.1080/15563650.2023.2212125
8. Busardò FP, Jones AW (2015) GHB pharmacology and toxicology: acute intoxication, concentrations in blood and urine in forensic cases and treatment of the withdrawal syndrome. Curr Neuropharmacol 13:47–70. https://doi.org/10.2174/1570159X13666141210215423
9. Boyer EW, Shannon M (2005) The serotonin syndrome. N Engl J Med 352:1112–1120. https://doi.org/10.1056/NEJMra041867
10. Wijdicks EFM, Ropper AH (2024) Neuroleptic malignant syndrome. N Engl J Med 391:1130–1138. https://doi.org/10.1056/NEJMra2404606
11. Eddleston M, Buckley NA, Eyer P, Dawson AH (2008) Management of acute organophosphorus pesticide poisoning. Lancet 371(9612):597–607
12. Seger DL (2006) A critical reconsideration of the clinical effects and treatment recommendations for sodium channel blocking drug cardiotoxicity. Toxicol Rev 25:283–296. https://doi.org/10.2165/00139709-200625040-00008